

SPOTLIGHT

Nuclear envelope lipids request border surveillance

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In this issue, Thaller et al. (2021. *J. Cell Biol.* <https://doi.org/10.1083/jcb.202004222>) explore how the ESCRT protein Chm7 is recruited to sites of defective nuclear pore assembly. They show that a lipid, phosphatidic acid, is enriched at pathological nuclear envelope herniations, where it promotes Chm7 recruitment for membrane surveillance and repair.

The membranes of the nucleus form a protective boundary around the DNA, while nuclear pore complexes (NPCs) embedded in these membranes act as control gates, deciding what can pass (1). Maintaining the integrity of this boundary, called the nuclear envelope (NE), is essential for cell survival. Complications can arise if the NE or its pores become disrupted. Cells employ a sophisticated surveillance system that can rapidly recognize and fix any damage inflicted on the NE. How this damage is located and what activates its repair is still poorly understood.

The integrity of the NE is compromised in a variety of conditions, including neurodegenerative diseases like amyotrophic lateral sclerosis and frontotemporal degeneration. An age-related decline in NE/NPC function has been observed (2). Moreover, a key feature of early onset dystonia, a disease that causes muscle spasms, is NE herniations that originate from NPC-like structures. Herniations are frequently observed in yeast cells with defects in NPC biogenesis. It is therefore thought that herniations result from defective NPC assembly.

Embedding new NPCs into the NE is not trivial. Interphase NPC assembly likely occurs through an inside-out evagination of the inner nuclear membrane (INM) followed by a membrane fusion with the outer nuclear membrane (3). This process creates holes in the NE and poses a threat to NE integrity if not properly executed.

Protection comes from an ESCRT-dependent surveillance system that is recruited by NE disruption or defective NPC assembly (4). In yeast, two key players are the ESCRT (endosomal sorting complexes required for transport) protein Chm7 and the LEM (LAP2-emerin-MAN1) domain protein Heh1. Heh1 and Chm7 are normally segregated to opposite sides of the NE. However, if the NE is damaged, Heh1 and Chm7 come in contact (5). Heh1 activates Chm7, which can then repair the damage to the NE by closing and sealing any gaps. Active Chm7/Heh1 may form a polymer similar to that of the human CHMP7-LEM2 complex (6). Several domains of Chm7 (the orthologue of mammalian CHMP7) contribute to its cellular localization and activity when NE surveillance is triggered. In this issue, Thaller et al. (7) shed light on the determinants controlling the timely recruitment of Chm7 to NE defect sites.

The researchers characterized a conserved hydrophobic region of Chm7, which is predicted to form an amphipathic helix. Amphipathic helices are found in numerous proteins and are defined by the separation of hydrophobic and polar residues between the two faces of the helix. This separation enables these helices to bind at apolar/polar interfaces such as the lipid surfaces of cell organelles. Depending on the nature and distribution of the hydrophobic and polar residues as well as the length of the helix, amphipathic helices can be tuned into versatile molecular tools and for example,

deform lipid bilayers, recognize specific lipids or sense membrane curvature.

Chm7 is normally located in the cytosol but can be forced into the nucleus and into interaction with Heh1 by inhibiting its nuclear export. Interestingly, Thaller et al. observed that mutating the hydrophobic face of the amphipathic helix inhibited Chm7 recruitment to the INM, where Heh1 is located, suggesting the existence of a previously unknown membrane-binding activity in Chm7. The authors employed *in vitro* assays using liposomes to elucidate what attracts Chm7 to membranes. Chm7 showed enhanced liposome binding when the concentration of phosphatidic acid (PA) was increased, suggesting that Chm7 binds directly to PA-rich lipid bilayers. Chm7 preferred liposomes with a small diameter and, hence, high curvature over larger liposomes with an essentially flat surface. Given that Chm7 bound to PA-rich membranes *in vitro*, the authors then analyzed how altered cellular PA levels affect Chm7 distribution. Interestingly, elevated PA levels led to a redistribution of Chm7 from the cytoplasm to the membranes of the NE and the endoplasmic reticulum, which required Chm7's amphipathic helix. Since increased PA levels can disrupt NE integrity, this raised the interesting possibility that Chm7 directly senses an instability in nuclear membranes via PA.

A key question that follows is whether PA indeed accumulates at sites of Chm7 activity. To probe INM PA levels, Thaller et al.

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took advantage of an INM-specific PA biosensor (8). This sensor comprises an amphipathic helix that specifically binds to the phosphate moiety of PA by a three-finger grip of basic residues. The PA sensor was nucleoplasmic under normal growth conditions, indicating low PA levels at the INM. In contrast, the PA sensor relocated to distinct INM foci when a constitutively active variant of Chm7 was expressed and colocalized with Chm7 at these foci. Thus, this hyperactive variant of Chm7 appears to affect INM PA levels, either by locally altering PA metabolism or through direct recruitment of PA, suggesting some positive feedback in PA-mediated Chm7 recruitment to membranes.

Wild-type Chm7 is known to accumulate at the NE when de novo NPC assembly is perturbed. A hallmark of several NPC assembly mutants is the occurrence of NE herniations. These aberrant structures likely arise as a consequence of impaired NE remodeling. Notably, the PA sensor accumulated in distinct foci along the nuclear periphery in a nuclear pore mutant that exhibits such herniations. Thaller et al. found that Chm7 was dispensable for this PA sensor accumulation. This suggested that a local increase in PA concentration likely

precedes Chm7 recruitment under conditions of NPC misassembly. Finally, through a series of elegant correlative light and electron microscopy experiments, the authors offered compelling ultrastructural evidence that the NPC misassembly-associated NE herniations can indeed recruit the PA sensor, indicative of high local PA concentrations at these sites (7).

Thaller et al. propose a model in which a specific lipid, PA, can request NE surveillance by Chm7. PA accumulates at NE herniations, which are indicative of NE damage, and recruits Chm7 via its PA-sensing amphipathic helix. Chm7 then binds to Heh1, which reinforces the membrane recruitment and activates Chm7.

This study is conceptually important and offers a lot of food for thought. First, because it adds a missing link—a lipid—to the complex hierarchy of signals that lead to NE surveillance and repair. Second, because it raises the question of which specific lipids surround NPCs in health and disease and how these lipids become locally enriched. And more generally, because it gives fresh insight into the poorly understood connection between lipid metabolism and the functional architecture of the nucleus (8, 9). Notably, Opi1, from which the PA sensor is

derived, not only senses PA but also senses the lipid-packing density of a membrane, which is related to its lipid saturation state (10). Hence, the SOS call from PA that Thaller et al. have now detected may just be the tip of the iceberg, with other lipid surveillance codes remaining to be discovered.

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